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APPLICATION NUMBER: *60/529,470*
FILING DATE: *December 15, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/42474*

UNITED STATES PATENT AND TRADEMARK OFFICE
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Todd Duncan	Campbell	Petaluma, California

Additional inventors are being named on the One *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Alginate Cap with Therapeutic and Cellular Components for Treating Vulnerable Plaque

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number:

OR

☒ Firm or Individual Name	James F. Hensel				
Address	2911 SW Orchard Hill Place				
Address					
City	Lake Oswego	State	OR	Zip	97035-1194
Country	USA	Telephone	503-244-3232	Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* Cover and 35 Pages

☒ Drawing(s) *Number of Sheets* Thirteen

☐ Application Date Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☒ A check or money order is enclosed to cover the filing fees.

☐ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number:

☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): $80

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME James F. Hensel

TELEPHONE 503-244-3232

Date December 15, 2003

REGISTRATION NO. *(if appropriate)*

Docket Number:

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Docket Number

INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle [if any]	Family or Surname	Residence (City and either State or Foreign Country)
James Finley	Hensel	Lake Oswego, Oregon

Number 1 of 1

13049 U.S.PTO
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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 80

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Todd Duncan Campbell
Examiner Name	
Art Unit	
Attorney Docket No.	

METHOD OF PAYMENT *(check all that apply)*

☑ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80

SUBTOTAL (1) ($) 80

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 0

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	James F. Hensel	*Registration No. (Attorney/Agent)*		*Telephone*	503-244-3232
Signature				*Date*	12/15/03

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Endolumen Therapeutics, Inc.
2911 SW Orchard Hill Place
Lake Oswego, OR 97035

December 15, 2003

Commissioner for Patents
Mail Stop Provisional Patent Application
Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

Via Express Mail

RE: Provisional Patent Application

Dear Commissioner:

Please find enclosed the following:

Provisional Patent Application Titled "ALGINATE CAP WITH THERAPEUTIC AND CELLULAR COMPONENTS FOR TREATING VULNERABLE PLAQUE" including:

a. Provisional Application Coversheet (two pages);
b. Fee Transmittal;
c. Specification consisting of a cover page and 35 additional pages;
d. Drawings consisting of 13 pages; and
e. Check payable to the Commissioner of Patents in the Amount of $80 (claiming small business entity status).

Warm regards,

James F. Hensel

U.S. PROVISIONAL PATENT APPLICATION

ALGINATE CAP WITH THERAPEUTIC AND CELLULAR COMPONENTS FOR TREATING VULNERABLE PLAQUE

INVENTORS

Name: Todd Duncan Campbell

Name: James Finley Hensel

CORRESPONDENCE:

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Lake Oswego, OR 97035-1194

ALGINATE CAP WITH THERAPEUTIC AND CELLULAR COMPONENTS FOR TREATING VULNERABLE PLAQUE

FIELD OF THE INVENTION

The present invention relates generally to treatment of vulnerable plaque, and more specifically to in-situ formed alginate caps with therapeutic and cellular components to cover vulnerable plaque in a vessel.

BACKGROUND OF THE INVENTION

Although the buildup of cholesterol and other fatty substances on blood vessel walls has received much attention in preventative measures and treatments for vascular diseases, the development and rupture of non-occlusive, soft atherosclerotic or vulnerable plaques in coronary arteries may be a larger contributor to myocardial infarction, known commonly as a heart attack.

Research suggests that vulnerable plaques have a dense infiltrate of macrophages within a thin fibrous cap that overlies a pool of lipid, a fat-like compound. Vulnerable plaque is formed from droplets of lipid that are absorbed by an artery, which can cause the release of proteins called cytokines that exacerbate inflammation. The cytokines act as an adhesive, attracting monocytes, so-called immune-system cells, to the artery wall where they push into the tissue of the wall. The monocytes change into macrophages, cells of the reticuloendothelial system, which begin to soak up fat droplets and form a plaque with a thin covering.

The rupture of the thin covering of the vulnerable plaques, due to inflammatory processes and mechanical stress like increased blood pressure, results in the thin covering over the plaque cracking and exposing blood to the lipid core and other plaque components. Vulnerable plaque erodes or ruptures, creating a raw tissue surface that forms scabs, and pieces of plaque that break off may accumulate in the coronary artery to create a thrombus of sufficient size to slow down or stop blood flow.

Vulnerable plaque is ingrained under the arterial wall and is difficult to detect with conventional means such as angiography or fluoroscopy. Thermography, which is capable of detecting a temperature difference between atherosclerotic plaque and healthy vessel walls, is one of the imaging methods being pursued for locating vulnerable plaque.

A significant amount of medical research continues to focus on the prevention and treatment of the softer vulnerable plaque, as well as the treatment of harder atherosclerotic plaque within vessels. One promising area of medical study is local drug delivery to diseased or traumatized treatment areas. For example, in an effort to prevent restenosis provoked by medical procedures, systems and methods have been developed to locally deliver pharmacological agents such as rapamycin, an immunosuppressant known for its anti-proliferation properties, or paclitaxel, a chemotherapy agent and microtubular stabilizer that causes cells to stop dividing due to a mitotic block between metaphase and anaphase of cell division. Some of these inhibitory pharmacological agents have the potential to interfere or delay healing, weakening the structure or elasticity of the newly healed vessel wall and damaging surrounding endothelium and/or other medial smooth muscle cells. Dead and dying cells release mitogenic agents that may stimulate additional smooth muscle cell proliferation and exacerbate stenosis.

The focused delivery of therapeutically effective drug levels is critical for optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug to neighboring cells. Thus, various systems for delivering pharmaceutical agents to a targeted area of a vessel wall have been proposed.

One drug-delivery system receiving much attention in recent years involves drug-eluting coatings for stents, which allow drugs to release during extended periods of time such as several weeks or months. For example, a medical device coating may express one or more therapeutic agents to inhibit smooth muscle cell proliferation, as described in "Implants Possessing a Surface of Endothelial Cells Genetically-Modified to Inhibit Intimal Thickening," Williams et al., U.S. Patent No. 5,957,972 granted September 28, 1999. The coating includes a monolayer of endothelial cells that are genetically modified to express the therapeutic agents and most specifically, the protein interferon-gamma.

An anti-thrombogenic, lubricious coating for metallic medical devices has been developed to release sustained, therapeutic amounts of nitric oxide, as disclosed in "Nitric Oxide-Releasing Metallic Medical Devices," Fitzhugh et al., U.S. Patent No. 6,270,779 granted August 7, 2001.

Researchers are trying to construct softer and more flexible implant stents of shaped polymeric hydrogels, as suggested in "Medical Devices Comprising Ionically and Non-Ionically Crosslinked Polymer Hydrogels Having Improved Mechanical Properties," Ronan et al., U.S. Patent No. 6,387,978 issued May 14, 2002. Some of these polymeric hydrogel stents are at least partially bioabsorbable, as disclosed in "Stent-Graft with Bioabsorbable Structural Support," Burnside et al., U.S. Patent No. 6,626,939 issued September 30, 2003.

Biodegradable polymeric liners have been cast in situ for supporting an prostatic urethra, as disclosed in "Compositions, Methods and Devices for Treatment of Urethral Disorders," Slepian et al., U.S. Patent Application No. 2003/0103932 published June 5, 2003. The lining supports the urethra and peri-urethral tissue during healing and then biodegrades. Alternatively, the polymer coating is applied to a structural material such as a stent, to decrease adhesion and/or provide release of drugs to enhance healing. Polymers may be selected to minimize inflammation, secondary bleeding and late fibrotic scarring and stricturing.

Biodegradable polymers have also been used to cover and seal an interior surface area of a tissue lumen, described in "Biodegradable Polymeric Endoluminal Sealing Process, Apparatus and Polymeric Products for Use Therein," Slepian et al., U.S. Patent No. 6,443,941 granted September 3, 2002. The polymer may be delivered as a monomer or prepolymer solution, or as an at least partially preformed layer on a catheter balloon.

Despite all the advances in the percutaneous procedures and endoluminal treatments mentioned above, inflammation and damage to vessel tissue continue to be a significant problem. Therefore, the need remains for improved systems, methods and devices for treating diseased blood vessels, minimizing or eliminating damage to surrounding tissue during procedures, and preventing inflammation of diseased areas. The desirable treatment of specific tissues provides sustained local delivery of therapeutic

compositions to help tissue to heal while avoiding excessive drug levels. More specifically, improved methods and devices for treating vulnerable plaque protect diseased areas from rupture, minimize inflammation, control the dosage and delivery of therapeutic components over extended periods of time; and treat or prevent undesirable medical conditions within a vessel.

SUMMARY OF THE INVENTION

One aspect of the invention is an alginate cap for vulnerable plaque in a vessel of a mammalian body. The alginate cap includes an alginate matrix in contact with the vulnerable plaque and an endoluminal wall of the vessel, with a central lumen axially extending through the alginate matrix to allow fluid flow through the vessel while the alginate matrix covers the vulnerable plaque.

Another aspect of the invention is a method of treating vulnerable plaque in a vessel of a mammalian body. An alginate cap is formed within the vessel, and a therapeutic agent is eluted from one of a therapeutic component or a cellular component dispersed within the alginate cap. The alginate cap is in contact with the vulnerable plaque and an endoluminal wall of the vessel, and has a central lumen axially extending through the alginate cap.

Another aspect of the invention is a system for treating vulnerable plaque in a vessel of a mammalian body, including a cap formation catheter having a catheter body, a dog-boned formation balloon attached to the catheter body near a distal end of the catheter body, and an alginate-delivery lumen within the catheter body. An alginate cap is formed over the vulnerable plaque from an alginate solution injected through the alginate-delivery lumen into a cavity between the formation balloon and an endoluminal wall of the vessel when the formation balloon is inflated.

Another aspect of the invention is a method of forming an alginate cap in a vessel of a mammalian body. A cap formation catheter having a catheter body is positioned in the vessel. A dog-boned formation balloon attached to the catheter body near a distal end of the catheter body is inflated. An alginate solution is injected through an alginate-delivery lumen into a cavity formed between the inflated formation balloon and an

endoluminal wall of the vessel. The alginate solution is hardened to form the alginate cap over vulnerable plaque in a portion of the vessel.

Another aspect of the invention is a system for treating vulnerable plaque in a vessel of a mammalian body. The system includes a cap formation catheter having a catheter body. A distal occlusion balloon is attached to the catheter body near a distal end of the catheter body. A proximal occlusion balloon is attached to the catheter body proximal to the distal occlusion balloon. A medial formation balloon is attached to the catheter body between the distal occlusion balloon and the proximal occlusion balloon. An alginate-delivery lumen is included within the catheter body. An alginate cap is formed over the vulnerable plaque from an alginate solution injected through the alginate-delivery lumen into a cavity between the medial formation balloon and an endoluminal wall of the vessel when the distal occlusion balloon and the proximal occlusion balloon are inflated.

Another aspect of the invention is a method of forming an alginate cap in a vessel of a mammalian body. In this embodiment, a cap formation catheter having a catheter body is positioned in the vessel. A distal occlusion balloon attached to the catheter body near a distal end of the catheter body is inflated and a proximal occlusion balloon attached to the catheter body proximal to the distal balloon is inflated. A medial formation balloon attached to the catheter body between the distal occlusion balloon and the proximal occlusion balloon is inflated. An alginate solution is injected through an alginate-delivery lumen into a cavity formed between the inflated distal occlusion balloon, the inflated proximal occlusion balloon, the inflated medial formation balloon, and an endoluminal wall of the vessel. The alginate solution is hardened to form the alginate cap to cover the vulnerable plaque in a portion of the vessel.

Another aspect of the invention is a system for forming an alginate cap in a mammalian body, including a cap formation catheter having a catheter body, an angioplasty balloon attached to the catheter body near a distal end of the catheter body, a formation balloon attached to the catheter body proximal to the angioplasty balloon, and an alginate-delivery lumen within the catheter body. An alginate linking agent is disposed on a surface of the angioplasty balloon. An alginate cap is formed over the

vulnerable plaque from an alginate solution injected through the alginate-delivery lumen into a cavity between the formation balloon and an endoluminal wall of the vessel when the formation balloon is inflated.

Another aspect of the invention is a method of forming an alginate cap in a vessel of a mammalian body. In this embodiment, a cap formation catheter having a catheter body is positioned at a first location in the vessel. An angioplasty balloon attached to the catheter body near a distal end of the catheter and having an alginate linking agent disposed on a surface of the angioplasty balloon is inflated. The alginate linking agent is deposited on an endoluminal wall of the vessel. The angioplasty balloon is deflated and repositioned at a second location in the vessel distal to the first location. The angioplasty balloon is re-inflated. A formation balloon attached to the catheter body proximal to the angioplasty balloon is inflated. An alginate solution is injected through an alginate-delivery lumen into a cavity formed between the formation balloon and an endoluminal wall of the vessel. The alginate solution is hardened by the alginate linking agent deposited on the endoluminal wall of the vessel, and the vulnerable plaque in a portion of the vessel is covered.

Another aspect of the invention is a system for forming an alginate cap in a vessel of a mammalian body, including a cap formation catheter having a catheter body and an alginate-delivery lumen within the catheter body, and at least one formation balloon attached proximal to a distal end of the catheter body. An alginate cap is formed in the vessel when the cap formation catheter is inserted into the vessel and an alginate solution is injected through the alginate-delivery lumen into a cavity formed between the formation balloon and an endoluminal wall of the vessel.

Another aspect of the invention is a method of forming an alginate cap in a vessel of a mammalian body. A cap formation catheter with at least one formation balloon is inserted into the vessel. An alginate solution is injected into a cavity formed between the formation balloon and an endoluminal wall of the vessel when the formation balloon is inflated. The alginate solution is hardened to form the alginate cap, and the cap formation catheter is withdrawn from the vessel. The formed alginate cap is in contact

with the endoluminal wall of the vessel and includes a central lumen axially extending through the alginate cap.

BRIEF DESCRIPTION OF THE DRAWINGS

The aforementioned, and other features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention rather than limiting, the scope of the invention being defined by the appended claims and equivalents thereof. Various embodiments of the present invention are illustrated by the accompanying figures, the figures not necessarily drawn to scale, wherein:

FIG. 1 illustrates a system for treating vulnerable plaque in a vessel of a mammalian body, in accordance with one embodiment of the current invention;

FIG. 2 illustrates a longitudinal cross-sectional view of an alginate cap, in accordance with one embodiment of the current invention;

FIG. 3 illustrates a cross-sectional view of the alginate cap of **FIG. 2**;

FIG. 4 is a flow diagram of a method for treating vulnerable plaque in a vessel of a mammalian body, in accordance with another embodiment of the current invention;

FIG. 5 illustrates a longitudinal cross-sectional view of an alginate cap being formed within a vessel of a mammalian body, in accordance with one embodiment of the current invention;

FIG. 6 illustrates a longitudinal cross-sectional view of an alginate cap formed within a vessel of a mammalian body, in accordance with one embodiment of the current invention;

FIG. 7 is a flow diagram of a method for forming an alginate cap in a vessel of a mammalian body, in accordance with one embodiment of the current invention;

FIG. 8 illustrates a longitudinal cross-sectional view of an alginate cap being formed within a vessel of a mammalian body, in accordance with another embodiment of the current invention;

FIG. 9 illustrates a longitudinal cross-sectional view of an alginate cap formed within a vessel of a mammalian body, in accordance with another embodiment of the current invention;

FIG. 10 is a flow diagram of a method for forming an alginate cap in a vessel of a mammalian body, in accordance with another embodiment of the current invention;

FIG. 11a, **FIG. 11b**, **FIG. 11c**, **FIG. 11d**, **FIG. 11e**, and **FIG. 11f** illustrate longitudinal cross-sectional views of an alginate cap corresponding to steps in a method of forming an alginate cap, in accordance with another embodiment of the current invention;

FIG. 12 illustrates a longitudinal cross-sectional view of an alginate cap formed within a vessel of a mammalian body, in accordance with another embodiment of the current invention; and

FIG. 13 is a flow diagram of a method for forming an alginate cap in a vessel of a mammalian body, in accordance with another embodiment of the current invention.

DETAILED DESCRIPTION OF THE INVENTION

FIG. 1 illustrates a system for treating vulnerable plaque in a vessel **50** of a mammalian body **52**, in accordance with one embodiment of the present invention. The system includes a cap formation catheter **10** having a catheter body **12**. One or more inflatable balloons such as a dog-boned formation balloon **20** are attached to catheter body **12** near a distal end **14** of catheter body **12**. Alginate cap **30** is formed from an alginate solution **60** injected through an alginate-delivery lumen **18** of catheter body **12** into a portion **56** of vessel **50** to cover vulnerable plague **58**. Alginate solution **60** is injected into a cavity **22** between formation balloon **20** and an endoluminal wall **54** of vessel **50** when formation balloon **20** is inflated.

The formed alginate cap **30** includes an alginate matrix **32** that is in contact with endoluminal wall **54** of vessel **50** and covers vulnerable plaque **58**. A central lumen **42** axially extending through alginate matrix **32** permits fluids to flow through vessel **50**.

Inflation lumens within catheter body **12** allow an inflation fluid **48** to be transported from a proximal end **16** of cap formation catheter **10** into and out of the

interior regions of one or more inflation balloons attached to catheter body **12**. When cap formation catheter **10** is appropriately positioned within vessel **50**, exemplary alginate cap **30** is formed by inflating formation balloon **20**, creating a cavity **22** between an outer surface of formation balloon **20** and endoluminal wall **54** of vessel **50**. A guidewire **8** may be used to position cap formation catheter **10** at a desired location in body **52**, as is known in the art. Cap formation catheter **10** may have an over-the-wire, rapid exchange, monorail, or other type of catheter configuration, as is known in the art. An alginate solution **60** is injected through a port at proximal end **16**, through alginate-delivery lumen **18**, and into cavity **22**, where it hardens to form alginate cap **30** against endoluminal wall **54** of the vessel. Alginate cap **30** provides some mechanical support for vessel **50**, and may elute and locally deliver one or more therapeutic agents **40** from therapeutic and cellular components contained therein to treat vulnerable plaque **58** and nearby tissues.

Alginate cap **30** provides a mechanism for controlled, time-release characteristics of therapeutic agents **40** from any therapeutic components **34** and cellular components **36** within an alginate matrix **32** of alginate cap **30**. Delivery of therapeutic agents **40** may occur over days, weeks, months and even years after formation. In one embodiment, the invention provides localized delivery of one or more therapeutic agents **40** from therapeutic components **34** dispersed within alginate cap **30** when alginate cap **30** is formed within a vessel **50** of the mammalian recipient. In another embodiment, the invention provides long-term delivery of one or more therapeutic agents **40** via an alginate matrix **32** suitable for maintaining encapsulated cells and aggregates of viable cells from transplanted or implanted cells that produce such therapeutic agents.

Alginate cap **30** may include one or more therapeutic components **34** dispersed within alginate matrix **32**, which controls the elution of a therapeutic agent **40** from alginate cap **30**. Therapeutic component **34** includes, for example, an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, or a combination

thereof. Therapeutic agents **40** released from alginate cap **30** include, for example, therapeutic components **34** themselves or portions thereof.

Alternatively, alginate cap **30** may include one or more cellular components **36** dispersed within alginate matrix **32** to provide therapeutic agent **40**. Alginate matrix **32** provides an immune barrier for cellular components **36** and controls the elution of therapeutic agents **40** from alginate cap **30**. Cellular component **36** includes, for example, endothelial cells, manipulated cells of designer deoxyribonucleic acid, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, or a combination thereof. Therapeutic components **34** and cellular components **36** may elute one or more therapeutic agents **40** into surrounding tissue.

Alginate matrix **32** may include selected therapeutic components **34** and cellular components **36** that produce therapeutic agents **40** for elution from alginate matrix **32** of alginate cap **30**. When cellular components **36** are selected, alginate matrix **32** may serve as an immune barrier so that the immune system of the recipient does not recognize and destroy cellular component **36** contained within alginate matrix **32**, or terminate the production of therapeutic agents **40**. Meanwhile, alginate matrix **32** still allows for the metabolic transfer of nutrients, wastes, and therapeutic proteins and agents to pass through alginate matrix **32** into surrounding vessel **50**. Therapeutic agents **40** are delivered in close proximity to the treatment site and released from alginate cap **30**. Alginate cap **30** with therapeutic components **34** and cellular components **36** provides long-term expression of the therapeutic agents **40**.

Therapeutic agents **40** from cellular components **36** include, for example, a residue, a byproduct, or natural excretion from the cells. Therapeutic agents **40** include, for example, nitric oxide. Other examples of released therapeutic agents **40** include vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid-lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, a therapeutic component, a cellular component, or a combination thereof.

Alginate cap **30** having therapeutic components **34** or cellular components **36** may help prevent vulnerable-plaque erosion or rupture by eluting of one or more therapeutic agents **40** near the tissue needing treatment. For example, the eluted therapeutic agents may reduce inflammation in the vicinity of alginate cap **30** and within the treated area of vessel **50**.

Living cells or other biomaterials and therapeutic compounds may be immobilized in alginate matrix **32** such as an alginate gel. Cells immobilized in alginate gels maintain good viability during long-term culture, due in part to the mild environment of the gel network. Alginate gel provides a physically protective barrier for immobilized cells and tissue, and inhibits immunological reactions of the host. Alginate matrix **32** provides a location that is viable and productive for cellular components **36**, since alginate matrix **32** allows the diffusion of nutrients to the cell, diffusion of respiratory byproducts to the surrounding area, and diffusion of selected therapeutic components **34** in an unaltered condition from alginate matrix **32**. In some cases, alginate matrix **32** serves as an immune barrier while providing for diffusive transport for therapeutic and cellular materials. The immune barrier properties of alginate matrix **32** are particularly useful for non-host derived cell sources, or manipulated cells of designer deoxyribonucleic acid (DNA).

One example of a cellular component **36** is endothelial cells that produce nitric oxide, a regulating molecule for smooth muscle cell quiescence and maintenance of vascular smooth muscle cells in the non-proliferative stage. A patient's own endothelial cells from, for example, microvascular adipose tissue, may be harvested and mixed with an alginate solution, and formed along with alginate matrix **32** into alginate cap **30**. Upon implantation, the endothelial cells remain viable and locally produce nitric oxide to regulate and maintain the quiescent nature of smooth muscle cells, which can be a contributor to the production and recruitment of fibroblasts from the media and adventitia of arteries. With the continued long-term production of nitric oxide from the translocated endothelial cells, vascular patency may be maintained for a substantially longer period following cap formation.

Long-term administration of at least one therapeutic agent **40** such as nitric oxide may be provided to vessel **50** that is diseased or traumatized. For example, disruption of the endothelial lining in a diseased portion of vessel **50** may result in the reduction of nitric oxide production, leading to the loss of regulation of the smooth muscle cells. Endothelial-derived nitric oxide is a naturally occurring regulation compound. The endothelial cell lining of vessels **50** produces the nitric oxide molecule. Endogenously produced nitric oxide is produced by the endothelial cell in such a manner that the uptake of the molecule regulates the proliferation of the vascular smooth muscle cells and maintains the cellular quiescence of smooth muscle cells within the vascular architecture. Nitric oxide is critical to numerous biological processes, including vasodilation, neurotransmission, and macrophage-mediated microorganism and tumor killing. Nitric oxide may be administrated in a chemically synthesized form as a nitric oxide donor, such as nitroglycerin dispersed within alginate matrix **32**.

Since it is such a small molecule, nitric oxide is able to diffuse rapidly across cell membranes and, depending on the conditions, is able to diffuse distances of more than several hundred microns, as is demonstrated by its regulation of smooth muscle cells, vascular dilation, tissue compliance and physiological tone of the vessel. Nitric oxide may be produced within alginate matrix **32** and delivered directly to the vessel. For example, L-arginine, a naturally occurring amino acid, and other nutraceuticals may be converted to nitric oxide within alginate matrix **32** by a group of enzymes such as nitric oxide synthases. These enzymes convert L-arginine into citrulline, producing nitric oxide in the process. In another example, nitric oxide is liberated from diazeniumdiolates, compounds that release nitric oxide into the blood stream and vascular walls.

Alginate cap **30** comprises alginate matrix **32** with, for example, crosslinked chains of mannuronate alginate monomers **62** and guluronate alginate monomers **64**. A predetermined ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64** can be selected and formed into alginate matrix **32** to provide the desired elution rates for therapeutic agents **40**. Alginate, which may be extracted from brown seaweeds such as Phaeophyceae and Laminaria, is a linear copolymer with

homopolymeric blocks of mannuronate alginate monomers **62** and guluronate alginate monomers **64**, respectively, covalently linked together in different sequences or blocks.

Alginate matrix **32** may comprise a predetermined ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64**. The alginate monomers can appear in homopolymeric blocks of consecutive guluronate alginate monomers **64**, consecutive mannuronate alginate monomers **62**, alternating mannuronate alginate monomers **62** and guluronate alginate monomers **64**, or randomly organized blocks. The relative amount of each block type varies with the origin of the alginate. Alternating blocks of mannuronate alginate monomers **62** and guluronate alginate monomers **64** form the most flexible chains and are more soluble at lower pH than the other block configurations. Blocks of guluronate alginate monomers **64** form stiffer chain elements, and two guluronate alginate monomeric blocks of more than six monomers each form stable crosslinked junctions with divalent cations such as Ca2+, Ba2+, Sr2+, and Mg2+ leading to a three-dimensional gel network or alginate matrix.

At low pH, protonized alginates form acidic gels. The homopolymeric blocks form the majority of the junctions, and the relative content of guluronate alginate monomers **64** determines the stability of the gel.

Alginate gels can develop and set at temperatures close to room temperature. This property is particularly useful in applications involving fragile materials like cells or tissue with low tolerance for higher temperatures.

The alginate polymers serve as thermally stable cold-setting gelling agents in the presence of divalent cations such as calcium ions from calcium sources. Gelling depends on the ion binding, with the divalent cation addition being important for the production of homogeneous gels, for example, by ionic diffusion or controlled acidification of calcium carbonate. High guluronate alginate monomer content may produce strong, brittle gels with good heat stability, whereas high mannuronate alginate monomer content produces weaker, more elastic gels. At low or very high divalent calcium concentrations, high mannuronate alginates produce stronger gels. When the average chain lengths are not particularly short, the gelling properties correlate with the average guluronate alginate monomer block length having an optimum block size of about twelve monomers, and do

not necessarily correlate with the ratio of mannuronate alginate monomers **62** to guluronate alginate monomers **64**, which may be due primarily to alternating mannuronate-guluronate chains. Recombinant epimerases with different specificities may be used to tailor mechanical and transport characteristics of the alginate.

The solubility and water-holding capacity of the alginate depends at least on pH, molecular weight, ionic strength, and the nature of the ions present. Alginate tends to precipitate below a pH of about 3.5. Alginate with lower molecular weight calcium alginate chains of less than 500 monomers shows increasing water binding with increasing size. Lower ionic strength of alginate increases the extended nature of the calcium alginate chains. An alginate gel develops rapidly in the presence of divalent cations like Ca2+, Ba2+, Sr2+, or Mg2+ and acid gels may also develop at low pH. Gelling of the alginate premix occurs when divalent cations take part in the interchain ionic binding between guluronate alginate monomer blocks in the polymer chain, giving rise to a three-dimensional network. Alginates with a high content of guluronate alginate monomer blocks tend to induce stronger gels. Gels made of mannuronate-rich alginate are often softer and more fragile, with a lower porosity, due in part to the lower binding strength between the polymer chains and to the higher flexibilities of the molecules.

The gelling process is highly dependent on diffusion of gelling ions into the polymer network. Methods that may be used for the preparation of alginate gels include dialysis/diffusion and internal gelling.

In the dialysis/diffusion or diffusion-setting method, gelling ions are allowed to diffuse into the alginate solution. This method is commonly used for immobilization of living cells in the alginate gel. An alginate solution can also be solidified by internal gelation, internal setting, or in situ gelling. A calcium salt with limited solubility or complexed Ca2+-ions may be mixed into an alginate solution, resulting in the release of calcium ions, usually by the generation of acidic pH with a slowly acting acid such as D-glucono-α-lactone. The resultant alginate is a homogenous alginate macrogel. Diffusion setting and internal setting of the alginate matrix have different gelling kinetics and result in differences in their gel networks.

FIG. 2 illustrates a longitudinal view of an exemplary alginate cap, in accordance with one embodiment of the present invention. **FIG. 3** illustrates an axial cross-sectional view of the alginate cap of **FIG. 2**, with like-numbered elements referring to similar or identical elements in each illustration. **FIG. 2** and **FIG. 3** taken together, an alginate cap **30** includes an alginate matrix **32** and a central lumen **42** axially extending through alginate matrix **32**. Alginate cap **30** covers, for example, vulnerable plaque **58** in a portion of a vessel **50**. Alginate cap **30** may include one or more therapeutic components **34** and/or cellular components **36**. Therapeutic components **34** and cellular components **36** may be dispersed uniformly within alginate matrix **32** or have a preferred distribution. Therapeutic agents **40** are eluted from alginate cap **30**, wherein alginate matrix **32** controls the elution of therapeutic agents **40**. Alginate cap **30** provides a mechanism for controlled, time-release characteristics of therapeutic agents **40** from any therapeutic components **34** and cellular components **36** within an alginate matrix **32** of alginate cap **30**. In one embodiment, the invention provides localized delivery of one or more therapeutic agents **40** from therapeutic components **34** dispersed within alginate cap **30** when alginate cap **30** is formed within a vessel of a mammalian recipient. In another embodiment, the invention provides long-term delivery of one or more therapeutic agents **40** via a matrix suitable for maintaining encapsulated cells and aggregates of viable cells from transplanted or implanted cells that produce such therapeutic agents.

Alginate cap **30** may have crosslinked chains of mannuronate alginate monomers **62** and guluronate alginate monomers **64** in a predetermined ratio to provide the desired mechanical strength and flexibility while controlling the elution rates for therapeutic agents **40** from alginate cap **30**.

FIG. 3 illustrates an axial cross-sectional view of the alginate cap of **FIG. 2**, taken through line A-A'. Alginate cap **30** is in contact with an endoluminal wall **54** of a vessel **50**, and covers vulnerable plaque **58** in a portion of vessel **50**. Alginate cap **30** includes an alginate matrix **32** that may have one or more therapeutic components **34** or cellular components **36** dispersed therein. For example, therapeutic components **34** and cellular components **36** dispersed within alginate cap **30** may be uniformly dispersed throughout, have a non-uniform profile with a higher concentration of therapeutic

components **34** or cellular components **36** nearer the central lumen **42**, or have a non-uniform profile with a higher concentration of therapeutic components **34** and cellular components **36** closer to an outer surface of alginate cap **30**. In another example, therapeutic components **34** and cellular components agglomerate or collect in regions within alginate cap **30**.

FIG. 4 is a flow diagram of a method for treating vulnerable plaque in a vessel of a mammalian body, in accordance with another embodiment of the present invention. The method includes various steps to form an alginate cap, cover or cap vulnerable plaque in the vessel, and to treat or prevent one or more medical conditions in the region of alginate cap formation. The alginate cap includes an alginate matrix, and one or more therapeutic components and cellular components may be dispersed therein. Formation of the alginate cap may occur in a clinical setting, so that donor-provided cells, for example, may be harvested from a host or donor mammalian body and combined into the alginate solution immediately prior to formation of the alginate cap.

The alginate cap is formed within a vessel to cap vulnerable plaque and provide controlled, time-released delivery of therapeutic agents from either therapeutic components or cellular components dispersed within the alginate cap. In one embodiment, the alginate cap with an alginate matrix encapsulates and maintains the viability of cellular components, and allows the expression of therapeutic agents from the cells to pass through the alginate matrix and elute into surrounding target tissues such as arterial tissues.

Desired therapeutic components and cellular components are selected along with the desired quantity, as seen at block **100**. Selectable therapeutic components include, for example, an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, or a combination thereof. Selectable cellular components include, for example, endothelial cells, designer-DNA manipulated cells, host-derived cells from a

host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, or a combination thereof. The dose and constituency of added therapeutic and cellular components may be selected based on the desired treatment of the vessel and the desired elution rate of the therapeutic agents.

A ratio of mannuronate alginate monomers and guluronate alginate monomers may be determined to provide a predetermined elution characteristic of the alginate cap. Based on the desired elution characteristics of the therapeutic and cellular components, the ratio of mannuronate alginate monomers and guluronate alginate monomers may be determined. For example, the block length of mannuronate alginate monomers and the block length of guluronate alginate monomers are selected to achieve suitable strength and flexibility of the cap, while providing controlled delivery of therapeutic and cellular components dispersed within the alginate matrix.

Prior to injection and formation of the alginate cap, the alginate premix, monomers or polymers may be sterilized by passage through a selection of submicron filters, by exposure to radiation in the form of ionizing gamma or electron beams, or by other known methods of rendering a viscous solution sterile. The premix may be mixed in a suitable solvent prior to filtration and then dried, for example, by dialysis or spray drying.

An alginate solution including an alginate premix and an alginate solvent is mixed prior to forming the alginate cap, as seen at block **102**. In one example, the mannuronate alginate monomers, guluronate alginate monomers, and an alginate solvent such as alcohol or water are mixed to form the alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers. The concentration and viscosity of the alginate solution may be reduced with the addition of aqueous cellular or therapeutic components. In another example, the mannuronate alginate monomers, guluronate alginate monomers, alginate solvent, and the selected therapeutic or cellular components are combined to form the alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers. For example, endothelial cells are mixed into a formulation of alginate with appropriate mannuronate and guluronate components into an alginate solution, and the alginate

solution used to form the alginate cap. In another example, an alginate premix of mannuronate alginate monomers and guluronate alginate monomers, an alginate solvent such as alcohol or water, and one or more therapeutic components and cellular components are combined to form the alginate solution.

In an optional step, one or more viable cell components may be harvested from the host or a donor mammalian body, and incorporated or otherwise mixed into the alginate solution prior to formation of the alginate cap in the body, as seen at block **104**. The harvested cells may be further cultured to increase their numbers or further filtered to obtain the desired quantity, quality and type of cells. The harvested viable cellular component, such as endogenous endothelial cells, is mixed into the alginate solution prior to injecting the alginate solution. In another example, freeze-dried cells are mixed into the alginate solution with for, example, an aqueous-based alginate solvent. The freeze-dried cells are reconstituted when the alginate cap is formed within the body. In another example, cells from either a host or donor source are preserved with trehalose and freeze-dried, rendering the cells functional yet in a dehydrated state. Use of cells in a preserved fashion allows for mixing the alginate solution with the cells in advance or conjointly with the medical procedure. One skilled in the art can identify alternative cell-producing components that can be substituted for endothelial cells and provide therapeutic products from the alginate matrix.

A radiopaque additive such as divalent barium may be added to the alginate solution to improve fluoroscopic and radioscopic visualization of the alginate solution during formation of the alginate cap within the body.

An alginate linking agent is added to the alginate solution, as seen at block **106**. The added alginate linking agent comprises, for example, divalent calcium, divalent barium, divalent strontium, divalent magnesium, or a source of calcium such as a calcium salt. In one example, the alginate linking agent is added to the alginate solution immediately prior to injecting the alginate solution, due to rapid gelling and setting of the alginate matrix. In another example, the alginate linking agent is added to the alginate solution after injecting the alginate solution into the portion of the vessel. In another example, the alginate linking agent is co-injected into a portion of the vessel to form the

cap. In another example, the alginate linking agent is injected into the cap-formation cavity and combined with alginate solution injected from a separate port. In another example, the alginate linking agent is deposited, applied, diffused, or otherwise transferred to an endoluminal wall of the vessel prior to injecting the alginate solution into the portion of the vessel. As the alginate solution is injected, the alginate solution coagulates onto the vessel wall.

The alginate solution is injected into a cavity formed within a portion of the vessel, where the alginate solution crosslinks, gels, and hardens to form the alginate cap. The alginate cap is formed in contact with an endoluminal wall of the vessel and has a central lumen axially extending through the alginate cap. The amount of alginate solution injected into the cavity is related to the length and thickness of the formed cap. Crosslinking and polymerization of alginate solution may occur in situ while at body temperature, or activated with exposure to ultraviolet light, infrared light, or thermal energy.

The alginate solution may be injected into a portion of the vessel with a cap formation catheter. The cap formation catheter is positioned, for example, by advancing the distal end of the cap formation catheter to a treatment site using a guidewire inserted into the vessel, as is known in the art. When the cap formation catheter is positioned, the alginate cap may be formed with one or more formation balloons attached to the catheter body.

Once the alginate cap is formed, one or more therapeutic agents may be eluted from therapeutic or cellular components dispersed within the alginate cap, as seen at block **108**. In one example, the eluted therapeutic agent comprises nitric oxide from entrained endothelial cells to regulate the proliferation of smooth muscle cells in the vessel near the formed alginate cap. In another example, the cellular component in the alginate solution is reconstituted after the cellularized alginate cap is formed in the vessel, and therapeutic agents are produced and delivered to the vessel from the reconstituted cellular component. The immune barrier of the alginate matrix protects the cellular components. The alginate cap controls the elution of the therapeutic agent from therapeutic and cellular components within the matrix.

FIG. 5 illustrates a longitudinal cross-sectional view of an alginate cap **30** being formed within a vessel **50** of a mammalian body **52**, in accordance with one embodiment of the present invention. Vessel **50** has vulnerable plaque **58** in a portion **56** of vessel **50** that may partially block the flow of fluid. A cap formation catheter **10** with a catheter body **12** has a dog-boned formation balloon **20** attached to catheter body **12** near a distal end **14** of catheter body **12**. Formation balloon **20** is inflated, for example, with contrast fluid or inflation fluid **48** injected into an interior region of formation balloon **20**. An alginate-delivery lumen **18** within catheter body **12** delivers an alginate solution **60** into a cavity **22** formed between formation balloon **20** and an endoluminal wall **54** of vessel **50** when formation balloon **20** is inflated. Slots, grooves or flexible tubes are used, for example, to guide alginate solution **60** from alginate-delivery lumen **18** into cavity **22**.

As alginate solution **60** sets and hardens, alginate cap **30** with alginate matrix **32** and a central lumen **42** is formed within vessel **50** of body **52**. With alginate cap **30** formed in the stenosed region, vulnerable plaque **58** is covered and endoluminal walls **54** of vessel **50** may be locally expanded outward to reduce the constriction and allow for increased fluid flow.

FIG. 6 illustrates a longitudinal cross-sectional view of an alginate cap **30** formed within a vessel **50** of a mammalian body **52**, in accordance with one embodiment of the present invention and as described with respect to **FIG. 5**. Alginate cap **30** includes an alginate matrix **32** in contact with vulnerable plaque **58** and an endoluminal wall **54** of vessel **50**. Therapeutic agents **40** may be eluted from alginate cap **30** from one or more therapeutic components **34** and cellular components **36** dispersed within alginate matrix **32**. Eluted therapeutic agents **40** migrate into endoluminal wall **54** and other tissues near alginate cap **30** to provide desired therapeutic effects.

FIG. 7 is a flow diagram of a method of forming an alginate cap in a vessel of a mammalian body, in accordance with one embodiment of the present invention. The method includes various steps to form an alginate cap **30** as described with respect to **FIG. 5** and **FIG. 6**.

Cap formation catheter **10** is positioned within vessel **50**, as seen at block **120**. Cap formation catheter **10** has catheter body **12** with alginate-delivery lumen **18**.

Exemplary catheter body **12** has an inflation lumen for transporting inflation fluid **48** to inflate formation balloon **20**, and a guidewire lumen to aid in positioning cap formation catheter **10** within the body.

Dog-boned formation balloon **20** attached to catheter body **12** near a distal end **14** of catheter body **12** is inflated, as seen at block **122**. An inflation fluid or contrast fluid may be injected into formation balloon **20** to inflate and enlarge formation balloon **20**.

An alginate solution **60** is injected through alginate-delivery lumen **18** into cavity **22** formed between inflated formation balloon **20** and endoluminal wall **54** of vessel **50**, as seen at block **124**. Alginate solution **60** is hardened with an alginate linking agent to form alginate cap **30** within vessel **50**.

After alginate cap **30** has been formed, formation balloon **20** is deflated and withdrawn from vessel **50** along with cap formation catheter **10**, as seen at block **126**.

FIG. 8 illustrates a longitudinal cross-sectional view of an alginate cap **30** being formed within a vessel **50** of a mammalian body **52**, in accordance with another embodiment of the present invention.

Alginate cap **30** is formed in a vessel **50** of body **52** with a system that includes a cap formation catheter **10** having a catheter body **12**. A distal occlusion balloon **24** is attached to catheter body **12** near a distal end **14** of catheter body **12**. A proximal occlusion balloon **26** is attached to catheter body **12** proximal to distal occlusion balloon **24**. A medial formation balloon **28** is attached to catheter body **12** between distal occlusion balloon **24** and proximal occlusion balloon **26**. An alginate-delivery lumen **18** contained within catheter body **12** carries alginate solution **60** to treatable portion **56** of vessel **50**. Alginate cap **30** is formed over vulnerable plaque **58** from an alginate solution **60** injected through alginate-delivery lumen **18** into a cavity **22** between medial formation balloon **28** and an endoluminal wall **54** of vessel **50** when distal occlusion balloon **24** and proximal occlusion balloon **26** are inflated with an inflation fluid **48**. Slots, grooves or flexible tubes may be used to guide alginate solution **60** from alginate-delivery lumen **18** into cavity **22**.

FIG. 9 illustrates a longitudinal cross-sectional view of an alginate cap **30** formed within a vessel **50** of a mammalian body **52**, in accordance with another embodiment of

the present invention. Alginate cap **30** includes an alginate matrix **32** in contact with vulnerable plaque **58** an endoluminal wall **54** of vessel **50**, and may include one or more therapeutic components **34** or cellular components **36**. Therapeutic agents **40** are eluted from therapeutic components **34** and cellular components **36** dispersed within alginate matrix **32** of alginate cap **30**. Therapeutic agents **40** elute from alginate cap **30** through endoluminal wall **54** of vessel **50** and into various tissues of vessel **50** near formed alginate cap **30**.

FIG. 10 is a flow diagram of various steps for a method of forming alginate cap **30** in vessel **50** of mammalian body **52**, in accordance with another embodiment of the present invention, and as described with respect to **FIG. 8** and **FIG. 9**. Cap formation catheter **10** is positioned in vessel **50**, as seen at block **140**. Cap formation catheter **10** has catheter body **12**, alginate-delivery lumen **18**, and a plurality of inflation lumens.

Distal occlusion balloon **24** attached to catheter body **12** near distal end **14** of catheter body **12** is inflated, as seen at block **142**. Proximal occlusion balloon **26**, which is attached to catheter body **12** proximal to distal occlusion balloon **24**, is inflated. Medial formation balloon **28** attached to catheter body **12** between distal occlusion balloon **24** and proximal occlusion balloon **26** is inflated. Distal occlusion balloon **24** and proximal occlusion balloon **26** are inflated to occlude vessel **50**. Medial formation balloon **28** inflates to a diameter corresponding to the desired lumen diameter of alginate cap **30**.

Alginate solution **60** is injected through alginate-delivery lumen **18** into cavity **22** formed between inflated distal occlusion balloon **24**, inflated proximal occlusion balloon **26**, inflated medial formation balloon **28**, and endoluminal wall **54** of vessel **50**, as seen at block **144**. Alginate solution **60** hardens with an alginate linking agent to form alginate cap **30** over vulnerable plaque **58** within vessel **50**.

When alginate cap **30** forms, distal occlusion balloon **24**, proximal occlusion balloon **26**, and medial formation balloon **28** are deflated, and cap formation catheter **10** is withdrawn from vessel **50**, as seen at block **146**.

FIG. 11a, **FIG. 11b**, **FIG. 11c**, **FIG. 11d**, **FIG. 11e**, and **FIG. 11f** illustrate longitudinal cross-sectional views of an alginate cap corresponding to steps of a method

for forming an alginate cap **30**, in accordance with another embodiment of the present invention. The illustrative steps are performed with an alginate cap formation system to treat vulnerable plaque **58** in a portion **56** of a vessel **50** of a mammalian body **52**. The system includes a cap formation catheter **10** having a catheter body **12**. An angioplasty balloon **70** is attached to catheter body **12** near a distal end **14** of catheter body **12**. Angioplasty balloon **70** has an alginate linking agent **68** disposed on a surface **72** of angioplasty balloon **70**. A formation balloon **20** is attached to catheter body **12** proximal to angioplasty balloon **70**. An alginate-delivery lumen **18** is included within catheter body **12**. An alginate cap **30** is formed from an alginate solution **60** injected through alginate-delivery lumen **18** into a cavity **22** between formation balloon **20** and an endoluminal wall **54** of vessel **50** when formation balloon **20** is inflated.

Vessel **50** in body **52** having endoluminal wall **54** and one or more areas of vulnerable plaque **58** is illustrated in **FIG. 11a**. Cap formation catheter **10** is positioned at a first location **74** in vessel **50**, as seen in **FIG. 11b**. Cap formation catheter **10** has a catheter body **12**. A guidewire **8** inserted into body **52** may be used to guide cap formation catheter **10** to the desired position in vessel **50**, as is known in the art.

Angioplasty balloon **70** attached to catheter body **12** near distal end **14** of catheter body **12** is inflated with an inflation fluid **48**, as seen in **FIG. 11c**. When in contact with endoluminal wall **54**, alginate linking agent **68** disposed on surface **72** of angioplasty balloon **70** is deposited on or otherwise transferred onto vulnerable plaque **58** and endoluminal wall **54** of vessel **50**. In an alternative embodiment, alginate linking agent **68** is pre-deposited on an outer surface of formation balloon **20**, and transferred onto endoluminal wall **54** when formation balloon **20** is inflated.

Angioplasty balloon **70** is deflated, and cap formation catheter **10** is repositioned at a second location **76** in vessel **50**, as seen in **FIG. 11d**. Second location **76**, in this example, is distal to first location **74**.

Angioplasty balloon **70** is re-inflated, as seen in **FIG. 11e**. Re-inflated angioplasty balloon **70** serves as a distal protection device. Formation balloon **20** attached to catheter body **12** proximal to angioplasty balloon **70** is inflated. Alginate solution **60** is injected through alginate-delivery lumen **18** into a cavity **22** formed

between formation balloon **20** and endoluminal wall **54** of vessel **50**. Slots, grooves or flexible tubes are used, for example, to guide alginate solution **60** from alginate-delivery lumen **18** into cavity **22**. Alginate solution **60** is hardened, for example, by alginate linking agent **68** deposited on endoluminal wall **54** and vulnerable plaque **58** of vessel **50**.

Angioplasty balloon **70** and formation balloon **20** are deflated and withdrawn from vessel **50**, as seen in **FIG. 11f**. Angioplasty balloon **70** may be configured to capture any embolic particles **78** when angioplasty balloon **70** and formation balloon **20** are deflated.

FIG. 12 illustrates a longitudinal cross-sectional view of an alginate cap **30** formed within a vessel **50**, in accordance with another embodiment of the present invention. Alginate cap **30** includes an alginate matrix **32** in contact with an endoluminal wall **54** and vulnerable plaque **58** of vessel **50**. Therapeutic agents **40** are eluted from alginate cap **30** when one or more therapeutic components **34** and cellular components **36** are included within alginate matrix **32**. Eluted therapeutic agents **40** migrate into vulnerable plaque **58**, endoluminal wall **54** and other tissues near alginate cap **30** to provide a therapeutic effect.

FIG. 13 is a flow diagram of steps in a method for forming alginate cap **30** in vessel **50** of mammalian body **52**, in accordance with another embodiment of the present invention and described with respect to **FIG. 12** and **FIG. 13**.

Cap formation catheter **10** is positioned at first location **74** in vessel **50**, as seen at block **160**. Cap formation catheter **10** includes catheter body **12** with alginate-delivery lumen **18**.

Angioplasty balloon **70** attached to catheter body **12** near distal end **14** of catheter body **12** is inflated with inflation fluid **48**, as seen at block **162**. Angioplasty balloon **70** has alginate linking agent **68** disposed on surface **72** of angioplasty balloon **70**. Alginate linking agent **68** is deposited or otherwise transferred onto endoluminal wall **54** and vulnerable plaque **58** of vessel **50**.

Angioplasty balloon **70** is deflated by withdrawing inflation fluid **48** from an interior region, as seen at block **164**.

With angioplasty balloon **70** deflated to a reduced diameter, cap formation catheter **10** is repositioned at second location **76** located distally with respect to first location **74** in vessel **50**, as seen at block **166**. Angioplasty balloon **70** is re-inflated. Re-inflated angioplasty balloon **70** may serve as, for example, a distal protection device. A formation balloon **20** attached to catheter body **12** proximal to angioplasty balloon **70** is then inflated.

Alginate solution **60** is injected through alginate-delivery lumen **18** into cavity **22** formed between formation balloon **20** and endoluminal wall **54** of vessel **50**, as seen at block **168**. Alginate solution **60** is hardened or otherwise set to form alginate cap **30** and cover vulnerable plaque **58** in a portion **56** of vessel **50**. Alginate linking agent **68** previously deposited onto endoluminal wall **54** of vessel **50** hardens alginate solution **60**.

When alginate cap **30** is formed and hardened, angioplasty balloon **70** and formation balloon **20** are deflated and withdrawn from vessel **50**, as seen at block **170**. In one embodiment, angioplasty balloon **70** captures embolic particles **78** in a region of vessel **50** between angioplasty balloon **70** and formation balloon **20** when angioplasty balloon **70** and formation balloon **20** are deflated. For example, a proximal end of angioplasty balloon **70** encloses embolic particles **78** when deflated, and a distal end of formation balloon **20** encompasses the proximal end of angioplasty balloon **70** to retain embolic particles **78** while cap formation catheter **10** is being withdrawn. In another example, the proximal end of angioplasty balloon **70** includes a non-mobile calcium-rich surface that coagulates or crosslinks any alginate residuals, effectively capturing the residuals. Alternatively, embolic particles **78** may be aspirated out of vessel **50**, as is known in the art.

While the embodiments of the invention disclosed herein are presently considered to be preferred, various changes and modifications can be made without departing from the spirit and scope of the invention. For example, an alginate cap may provide similar protective and therapeutic benefits to other types of inflamed and diseased tissues within the body. The scope of the invention is indicated in the appended claims, and all changes that come within the meaning and range of equivalents are intended to be embraced therein.

CLAIMS

What is claimed is:

1. An alginate cap for vulnerable plaque in a vessel of a mammalian body, the alginate cap comprising:

an alginate matrix in contact with the vulnerable plaque and an endoluminal wall of the vessel; and

a central lumen axially extending through the alginate cap, wherein the central lumen of the alginate cap allows fluid flow in the vessel while the alginate matrix covers the vulnerable plaque.

2. The alginate cap of claim 1 wherein the alginate matrix is formed within the vessel from an alginate solution injected into a portion of the vessel.

3. The alginate cap of claim 1, wherein the alginate matrix comprises a predetermined ratio of mannuronate alginate monomers and guluronate alginate monomers.

4. The alginate cap of claim 1 further comprising:

a therapeutic component dispersed within the alginate matrix, wherein the alginate matrix controls the elution of a therapeutic agent from the alginate cap.

5. The alginate cap of claim 4, wherein the therapeutic component is selected from the group consisting of an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, and a combination thereof.

6. The alginate cap of claim 1 further comprising:

a cellular component dispersed within the alginate matrix, wherein the alginate matrix controls the elution of a therapeutic agent from the alginate cap.

7. The alginate cap of claim 6, wherein the cellular component is selected from the group consisting of endothelial cells, manipulated cells of designer deoxyribonucleic acid, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, and a combination thereof.

8. The alginate cap of claim 6, wherein the eluted therapeutic agent comprises nitric oxide.

9. The alginate cap of claim 6, wherein the eluted therapeutic agent comprises vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, a therapeutic component, a cellular component, and a combination thereof.

10. A method of treating vulnerable plaque in a vessel of a mammalian body, the method comprising:

forming an alginate cap within the vessel having a central lumen axially extending through the alginate cap, the alginate cap in contact with the vulnerable plaque and an endoluminal wall of the vessel; and

eluting a therapeutic agent from one of a therapeutic component or a cellular component dispersed within the alginate cap.

11. The method of claim 10 wherein the alginate cap controls the elution of the therapeutic agent.

12. The method of claim 10, wherein the eluted therapeutic agent is selected from the group consisting of vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, a therapeutic component, a cellular component, and a combination thereof.

13. The method of claim 10, wherein the eluted therapeutic agent comprises nitric oxide to regulate the proliferation of smooth muscle cells in the vessel near the formed alginate cap.

14. The method of claim 10 further comprising:

mixing an alginate solution including an alginate premix and an alginate solvent;

adding an alginate linking agent into the alginate solution; and

injecting the alginate solution into a portion of the vessel with a cap formation catheter.

15. The method of claim 14, wherein the alginate linking agent is added to the alginate solution prior to injecting the alginate solution into the portion of the vessel.

16. The method of claim 14, wherein the alginate linking agent is added to the alginate solution after injecting the alginate solution into the portion of the vessel.

17. The method of claim 14, wherein the alginate linking agent is deposited on an endoluminal wall of the vessel prior to injecting the alginate solution into the portion of the vessel.

18. The method of claim 14, wherein the added alginate linking agent comprises one of divalent calcium, divalent barium, divalent strontium, or divalent magnesium.

19. The method of claim 14 further comprising:

determining a ratio of mannuronate alginate monomers and guluronate alginate monomers to provide a predetermined elution characteristic of the alginate cap; and

combining mannuronate alginate monomers, guluronate alginate monomers, the alginate solvent, and the therapeutic component or the cellular component to form the alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers.

20. The method of claim 14 further comprising:

harvesting a viable cellular component from one of a host or a donor; and

mixing the harvested viable cellular component into the alginate solution prior to injecting the alginate solution.

21. The method of claim 20, wherein the harvested viable cellular component comprises endogenous endothelial cells.

22. The method of claim 10 further comprising:

reconstituting the cellular component in the alginate cap, wherein the eluted therapeutic agent is released from the reconstituted cellular component.

23. A system for treating vulnerable plaque in a vessel of a mammalian body, the system comprising:

a cap formation catheter having a catheter body;

a dog-boned formation balloon attached to the catheter body near a distal end of the catheter body; and

an alginate-delivery lumen within the catheter body, wherein an alginate cap is formed over the vulnerable plaque from an alginate solution injected through the alginate-delivery lumen into a cavity between the formation balloon and an endoluminal wall of the vessel when the formation balloon is inflated.

24. A method of forming an alginate cap in a vessel of a mammalian body, the method comprising:

positioning a cap formation catheter in the vessel, the cap formation catheter having a catheter body;

inflating a dog-boned formation balloon attached to the catheter body near a distal end of the catheter body;

injecting an alginate solution through an alginate-delivery lumen into a cavity formed between the inflated formation balloon and an endoluminal wall of the vessel; and

hardening the alginate solution to form the alginate cap, wherein the alginate cap covers vulnerable plaque in a portion of the vessel.

25. The method of claim 24 further comprising:

deflating the formation balloon; and

withdrawing the cap formation catheter from the vessel.

26. A system for treating vulnerable plaque in a vessel of a mammalian body, the system comprising:

a cap formation catheter having a catheter body;

a distal occlusion balloon attached to the catheter body near a distal end of the catheter body;

a proximal occlusion balloon attached to the catheter body proximal to the distal occlusion balloon;

a medial formation balloon attached to the catheter body between the distal occlusion balloon and the proximal occlusion balloon; and

an alginate-delivery lumen within the catheter body, wherein an alginate cap is formed over the vulnerable plaque from an alginate solution injected through the alginate-delivery lumen into a cavity between the medial formation balloon and an endoluminal wall of the vessel when the distal occlusion balloon and the proximal occlusion balloon are inflated.

27. A method of forming an alginate cap in a vessel of a mammalian body, the method comprising:

positioning a cap formation catheter in the vessel, the cap formation catheter having a catheter body;

inflating a distal occlusion balloon attached to the catheter body near a distal end of the catheter body;

inflating a proximal occlusion balloon attached to the catheter body proximal to the distal balloon;

inflating a medial formation balloon attached to the catheter body between the distal occlusion balloon and the proximal occlusion balloon;

injecting an alginate solution through an alginate-delivery lumen into a cavity formed between the inflated distal occlusion balloon, the inflated proximal occlusion balloon, the inflated medial formation balloon, and an endoluminal wall of the vessel; and

hardening the alginate solution to form the alginate cap, wherein the alginate cap covers vulnerable plaque in a portion of the vessel.

28. The method of claim 27 further comprising:

deflating the distal occlusion balloon, the proximal occlusion balloon, and the medial formation balloon; and

withdrawing the cap formation catheter from the vessel.

29. A system for treating vulnerable plaque in a vessel of a mammalian body, the system comprising:

a cap formation catheter having a catheter body;

an angioplasty balloon attached to the catheter body near a distal end of the catheter body, the angioplasty balloon having an alginate linking agent disposed on a surface of the angioplasty balloon;

a formation balloon attached to the catheter body proximal to the angioplasty balloon; and

an alginate-delivery lumen within the catheter body, wherein an alginate cap is formed over the vulnerable plaque from an alginate solution injected through the alginate-delivery lumen into a cavity between the formation balloon and an endoluminal wall of the vessel when the formation balloon is inflated.

30. A method of forming an alginate cap in a vessel of a mammalian body, the method comprising:

positioning a cap formation catheter at a first location in the vessel, the cap formation catheter having a catheter body;

inflating an angioplasty balloon attached to the catheter body near a distal end of the catheter body, the angioplasty balloon having an alginate linking agent disposed on a surface of the angioplasty balloon;

depositing the alginate linking agent on an endoluminal wall of the vessel;

deflating the angioplasty balloon;

repositioning the cap formation catheter at a second location in the vessel, the second location in the vessel distal to the first location in the vessel;

re-inflating the angioplasty balloon;

inflating a formation balloon attached to the catheter body proximal to the angioplasty balloon;

injecting an alginate solution through an alginate-delivery lumen into a cavity formed between the formation balloon and an endoluminal wall of the vessel; and

hardening the alginate solution to form the alginate cap, wherein the alginate solution is hardened by the alginate linking agent deposited on the endoluminal wall of the vessel, wherein the alginate cap covers vulnerable plaque in a portion of the vessel.

31. The method of claim 30, wherein the re-inflated angioplasty balloon serves as a distal protection device.

32. The method of claim 30 further comprising:

deflating the angioplasty balloon and the formation balloon; and

withdrawing the cap formation catheter from the vessel.

33. The method of claim 32, wherein the angioplasty balloon captures embolic particles when the angioplasty balloon and the formation balloon are deflated.

34. A system for forming an alginate cap in a vessel of a mammalian body, the system comprising:

a cap formation catheter having a catheter body and an alginate-delivery lumen within the catheter body; and

at least one formation balloon attached proximal to a distal end of the catheter body, wherein the alginate cap is formed in the vessel when the cap formation catheter is inserted into the vessel and an alginate solution is injected through the alginate-delivery lumen into a cavity formed between the formation balloon and an endoluminal wall of the vessel.

35. A method of forming an alginate cap in a vessel of a mammalian body, the method comprising:

inserting a cap formation catheter into the vessel, the cap formation catheter having at least one formation balloon;

injecting an alginate solution into a cavity formed between the formation balloon and an endoluminal wall of the vessel when the formation balloon is inflated;

hardening the alginate solution to form the alginate cap; and

withdrawing the cap formation catheter from the vessel, wherein the formed alginate cap is in contact with the endoluminal wall of the vessel and includes a central lumen axially extending through the alginate cap.

ABSTRACT OF THE DISCLOSURE

The invention provides an alginate cap for vulnerable plaque in a vessel of a mammalian body. The alginate cap includes an alginate matrix in contact with the vulnerable plaque and an endoluminal wall of the vessel. A central lumen extends axially through the alginate matrix. The central lumen of the alginate cap allows fluid flow in the vessel while the alginate matrix covers the vulnerable plaque. Methods and systems to form an alginate cap with the vessel and methods to treat the vessel are also disclosed.

FIG. 1

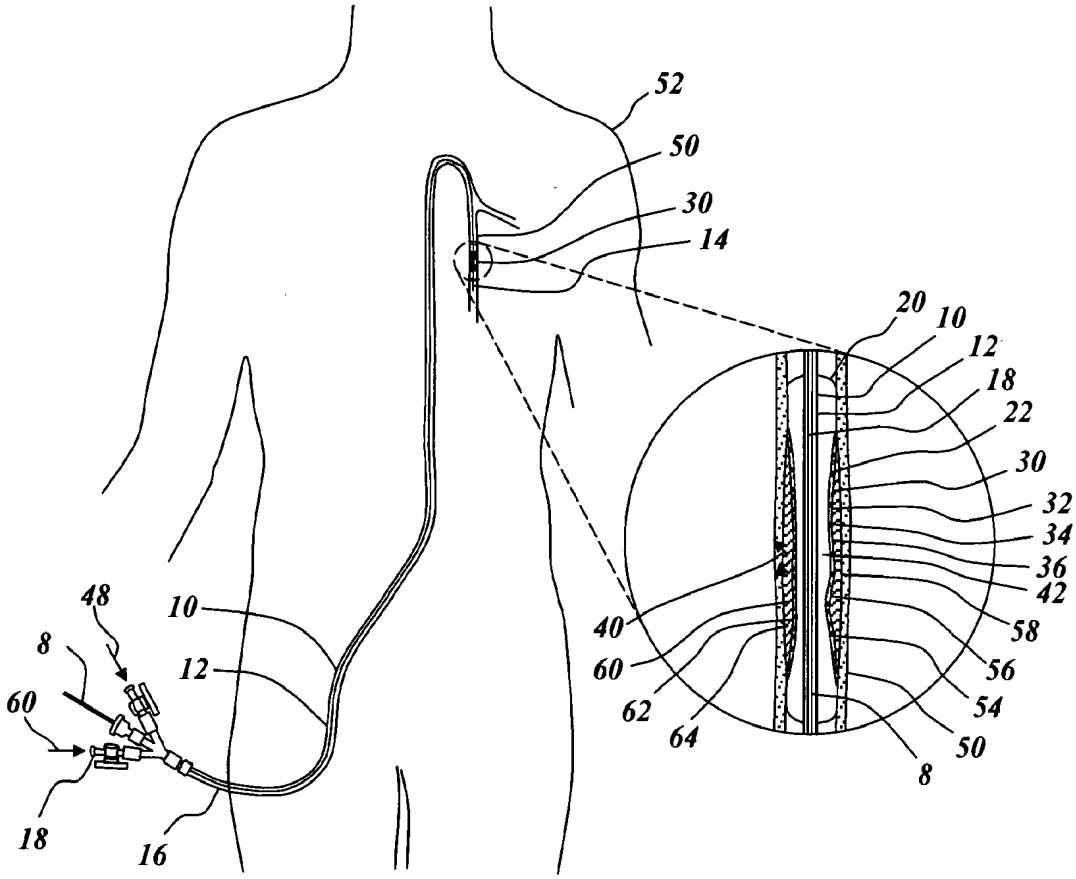
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FIG. 2

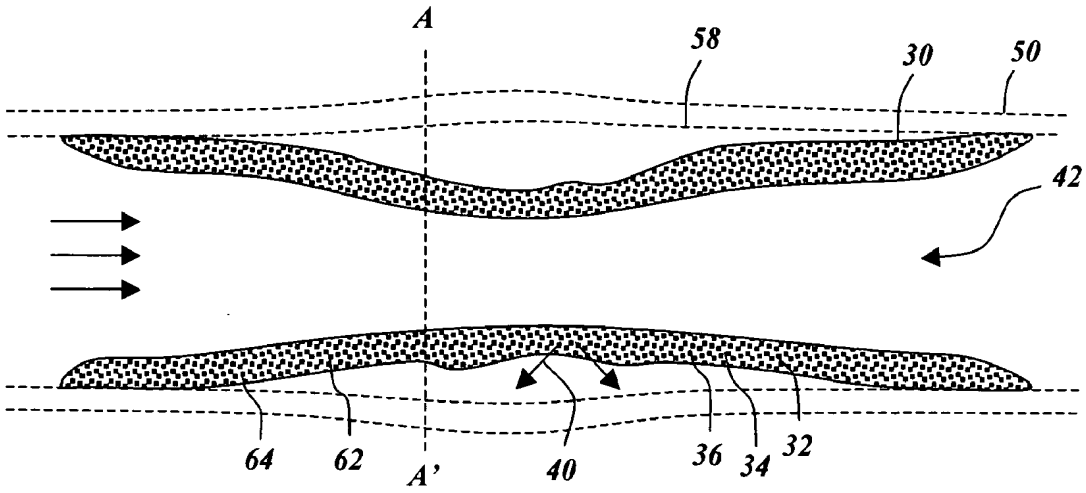


FIG. 3

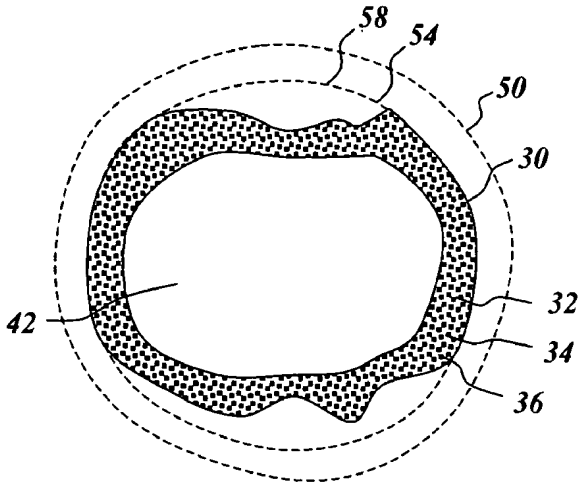


FIG. 4

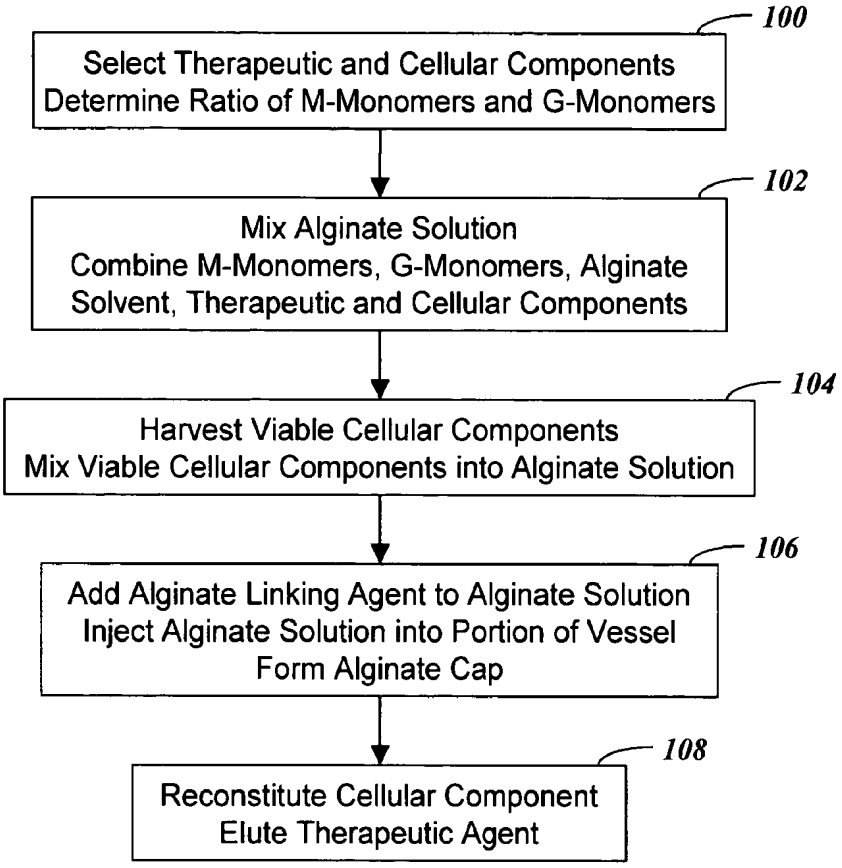

100
Select Therapeutic and Cellular Components
Determine Ratio of M-Monomers and G-Monomers
102
Mix Alginate Solution
Combine M-Monomers, G-Monomers, Alginate
Solvent, Therapeutic and Cellular Components
104
Harvest Viable Cellular Components
Mix Viable Cellular Components into Alginate Solution
106
Add Alginate Linking Agent to Alginate Solution
Inject Alginate Solution into Portion of Vessel
Form Alginate Cap
108
Reconstitute Cellular Component
Elute Therapeutic Agent

FIG 5

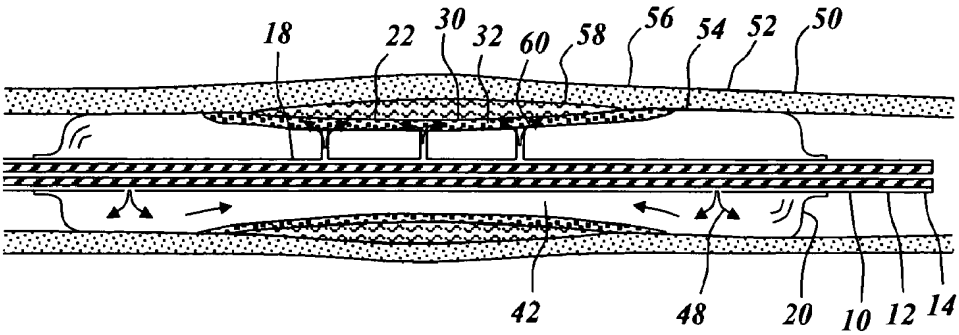


FIG. 6

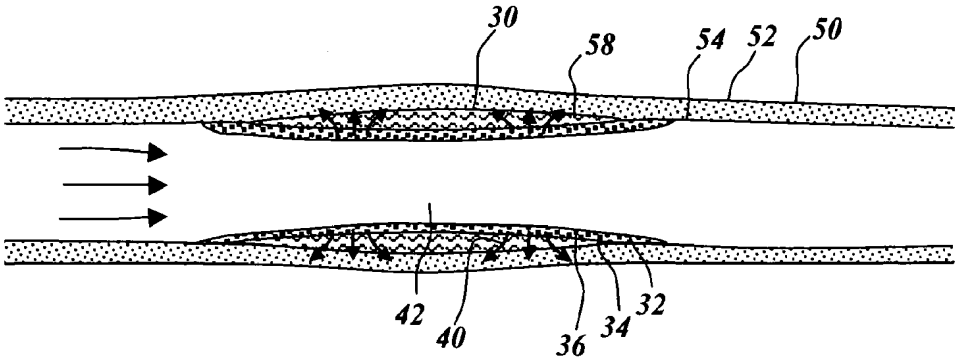


FIG. 7

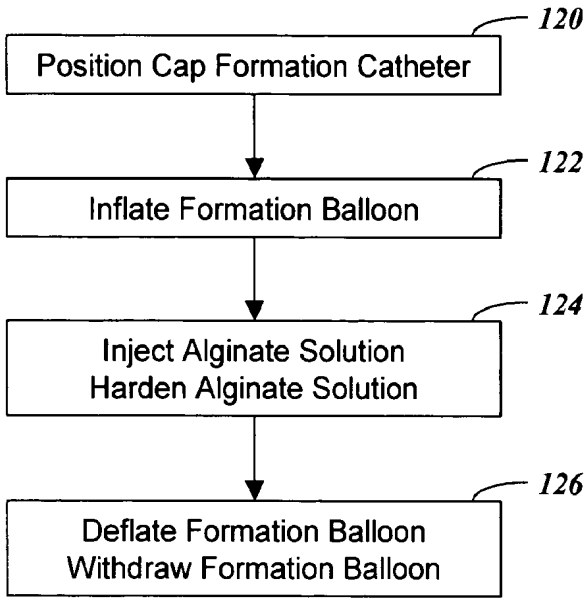

120
Position Cap Formation Catheter
122
Inflate Formation Balloon
124
Inject Alginate Solution
Harden Alginate Solution
126
Deflate Formation Balloon
Withdraw Formation Balloon

FIG. 8

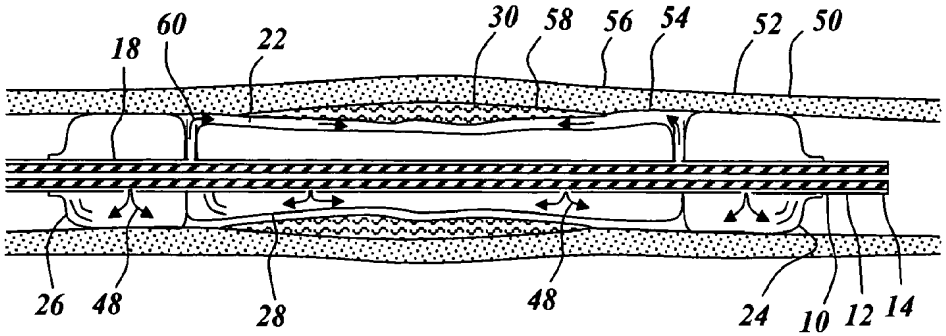


FIG. 9

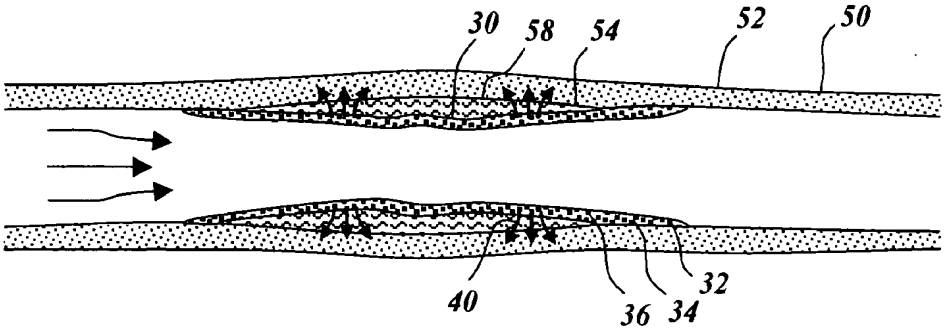


FIG. 10

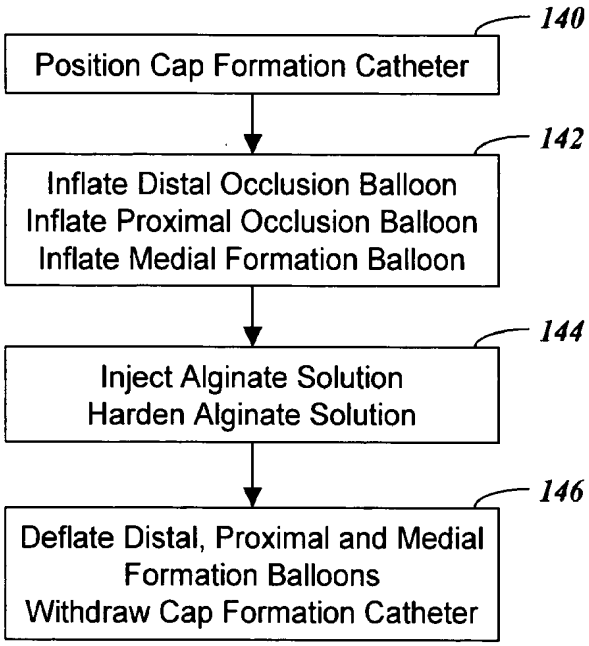

140
Position Cap Formation Catheter
142
Inflate Distal Occlusion Balloon
Inflate Proximal Occlusion Balloon
Inflate Medial Formation Balloon
144
Inject Alginate Solution
Harden Alginate Solution
146
Deflate Distal, Proximal and Medial Formation Balloons
Withdraw Cap Formation Catheter

FIG. 11a

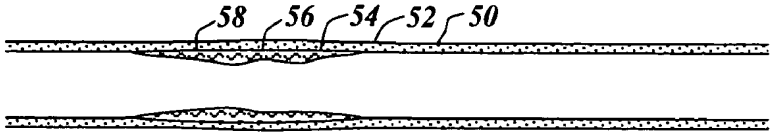


FIG. 11b

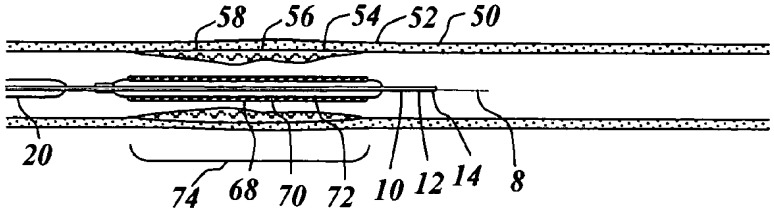


FIG. 11c

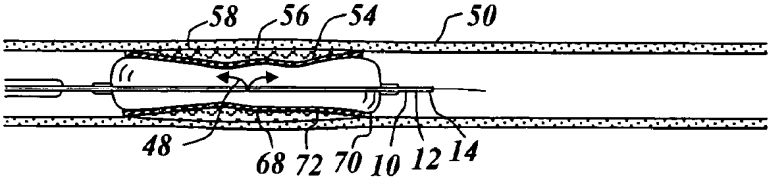


FIG. 11d

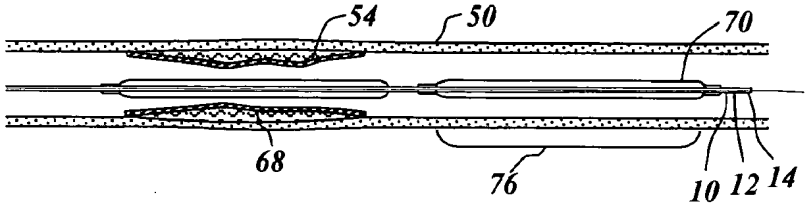


FIG. 11e

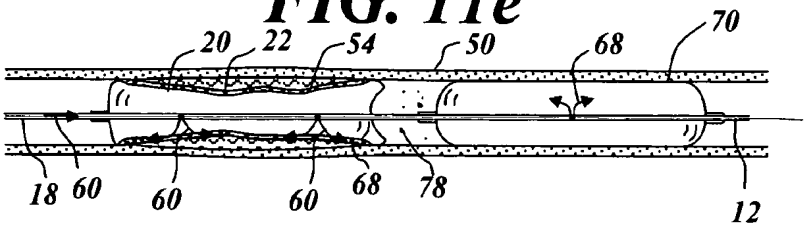


FIG. 11f

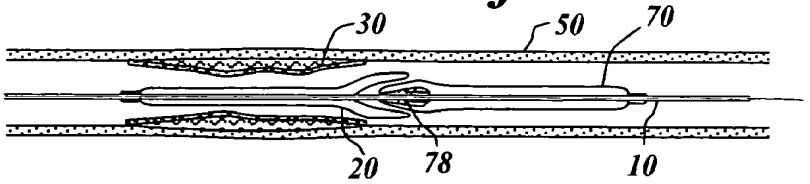


FIG 12

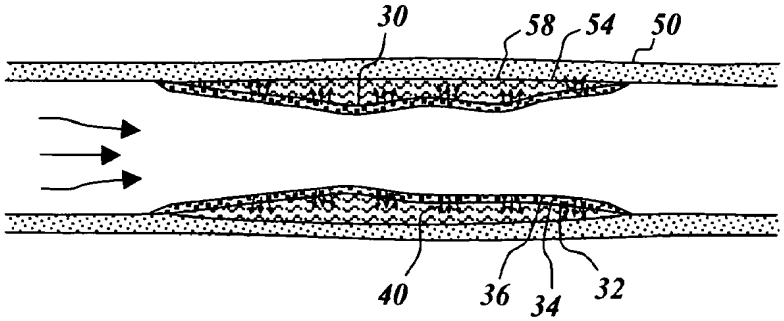
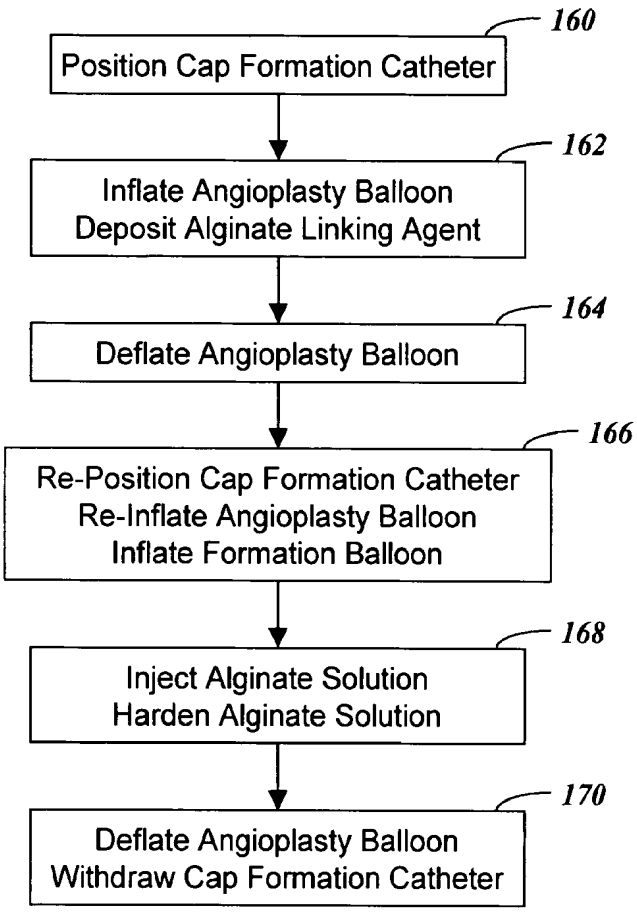


FIG. 13


160
Position Cap Formation Catheter
162
Inflate Angioplasty Balloon
Deposit Alginate Linking Agent
164
Deflate Angioplasty Balloon
166
Re-Position Cap Formation Catheter
Re-Inflate Angioplasty Balloon
Inflate Formation Balloon
168
Inject Alginate Solution
Harden Alginate Solution
170
Deflate Angioplasty Balloon
Withdraw Cap Formation Catheter